

Application No. 10/069,018

Supplemental Amendment dated December 19, 2003

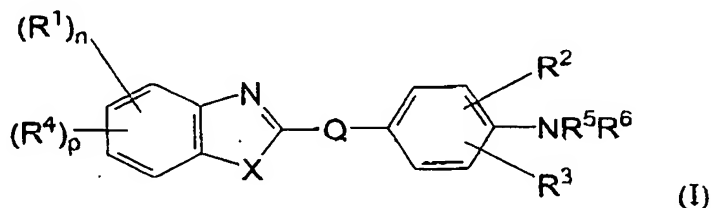
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**Amendments to the Claims:**

The following claims will replace all prior versions of the claims in this application (in the unlikely event that no claims follow herein, the previously pending claims will remain):

1-25. (Cancelled).

26. (Previously presented) An arylbenzazole compound represented by the structural formula I below, or a pharmaceutically acceptable salt thereof,



wherein

X represents S or O;

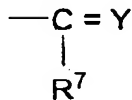
R<sup>1</sup> independently represents fluoro, iodo or trimethyltin;

R<sup>2</sup> represents hydrogen, NO<sub>2</sub>, N<sub>3</sub>, halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or CF<sub>3</sub>;

R<sup>3</sup> represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

R<sup>4</sup> independently represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

R<sup>5</sup> and R<sup>6</sup> each independently represent hydrogen, an amino acid, an alkyl, or a group



wherein Y represents O or S, and R<sup>7</sup> represents alkyl or -CH(R<sup>8</sup>)NH<sub>2</sub> where R<sup>8</sup> represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, -CH<sub>2</sub>- or -CH=CH-;

p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

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subject to the following provisos:

- (a) alkyl or substituted alkyl groups include linear, branched or cyclic structures but when present as linear or branched structures in the compound or as a moiety in another group such as alkoxy they are composed of less than ten carbon atoms;
- (b) p represents zero or 1 when n represents 3;
- (c) when n represents zero, at least one of R<sup>5</sup> or R<sup>6</sup> represents -C(Y)-CH(R<sup>8</sup>)NH<sub>2</sub>;
- (d) when a group is optionally substituted, unless otherwise specified, the substituent is selected from one or more of the following: a halogen, OH, SH, NH<sub>2</sub>, COOH and CONH<sub>2</sub>.

27. (Previously presented) An arylbenzazole compound of claim 26 with at least one of the following features:

- (a) alkyl groups when present as such or as a moiety in other groups such as alkoxy each contain less than six carbon atoms;
- (b) at least some alkyl groups when present as such or as a moiety in ether groups such as alkoxy are methyl or ethyl; or
- (c) halogen substituents, when present, are selected from fluorine, iodine, bromine and chlorine.

28. (Previously presented) An arylbenzazole compound of Claim 27 where the halogen substituent is fluorine.

29. (Currently amended) An arylbenzazole compound of Claim ~~29~~ 28 wherein the ~~compound incorporates the~~ said fluorine substituent is the isotope <sup>18</sup>F.

30. (Previously presented) An arylbenzazole compound of Claim 26 or 27 wherein R<sup>1</sup> is fluorine.

31. (Previously presented) An arylbenzazole compound of claim 26 wherein R<sup>1</sup> is in the 5-position of the benzazole moiety.

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32. (Previously presented) An arylbenzazole compound of claim 26 wherein  $R^2$  is a substituent in the 3' position of the phenyl group.
33. (Previously presented) An arylbenzazole compound of claim 26 wherein X is sulphur.
34. (Previously presented) An arylbenzazole compound of claim 26 wherein one of  $R^5$  and  $R^6$  is  $C(Y)-CH(R^8)NH_2$  or a salt thereof, and the other is hydrogen.
35. (Previously presented) An arylbenzazole compound of claim 26 wherein Y is O and  $R^8$  is selected from hydrogen,  $-CH_3$ ,  $-(CH_2)_4NH_2$  or  $-CH_2OH$ .
36. (Cancelled)
37. (Cancelled)
38. (Cancelled)
39. (Previously presented) An arylbenzazole compound which is one of the following:  
4 Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
6 Fluoro 2-(4'-amino-3'-methylphenyl)benzothiazole;  
4 Fluoro-2-(4'-aminophenyl)benzothiazole;  
6-Fluoro-2-(4'-aminophenyl)benzothiazole;  
4,5-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
4,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
5,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
7-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
6,7-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;

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5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole;  
5-Fluoro-2-(4'-aminophenyl)benzothiazole;  
4-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;  
5-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;  
6-Fluoro-2-(4'-amino-3'-iodophenyl)benzothiazole;  
4-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;  
5-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;  
6-Fluoro-2-(4'-amino-3'-chlorophenyl)benzothiazole;  
4-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;  
5-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;  
6-Fluoro-2-(4'-amino-3'-bromophenyl)benzothiazole;  
2-(4'-Aminophenyl)benzothiazole alanyl amide hydrochloride salt;  
2-(4'-Amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;  
2-(4'-Amino-3'-chlorophenyl)benzothiazole alanyl amide hydrochloride salt;  
2-(4'-Aminophenyl)benzothiazole lysyl amide dihydrochloride salt;  
2-(4'-Amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;  
2-(4'-Amino-3'-chlorophenyl)benzothiazole lysyl amide dihydrochloride salt;  
2-(4'-Amino-3'-methylphenyl)benzothiazole serine hydrochloride salt;  
6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;  
5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;  
6-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt;  
5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;  
5-Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole glycyl amide hydrochloride salt;  
5-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;  
7-Iodo-2-(4'-amino-3'-methylphenyl)benzothiazole;  
5-Fluoro-2-(4'-acetamido-3'-methylphenyl)benzothiazole;  
5-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;  
4-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;  
6-Fluoro-2-(4'-amino-3'-cyanophenyl)benzothiazole;

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5-Fluoro-2-(4'-amino-3'-(hydroxymethyl)phenyl)benzothiazole;  
5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole alanyl amide hydrochloride salt;  
5,6-Difluoro-2-(4'-amino-3'-methylphenyl)benzothiazole lysyl amide dihydrochloride salt; and  
5-Trimethylstannyl-2-(4'-amino-3'-methylphenyl)benzothiazole.

40. (Previously presented) An arylbenzazole compound of claim 26 for use in therapy as an active therapeutic substance wherein said arylbenzazole compound is an acid addition salt derived from an acid selected from the group consisting of: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, p-toluenesulphonic, tartaric, citric, lactobionic, formic, malonic, pantothenic, succinic, naphthalene-2-sulphonic, benzenesulphonic, methanesulphonic and ethanesulphonic.

41. (Previously presented) A isotopically labelled arylbenzazole compound selected from the group consisting of 5-<sup>18</sup>Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole and 6-<sup>18</sup>Fluoro-2-(4'-amino-3'-methylphenyl)benzothiazole.

42. (Currently amended) A pharmaceutical formulation ~~for medical use~~ comprising a compound of claim 26 and a pharmaceutically acceptable carrier.

43. (Currently amended ) A medical preparation comprising: a therapeutically effective ~~non-toxic~~ amount of a compound of claim 26 and a pharmaceutically inert excipient.

44. (Previously presented) A unit dosage of a pharmaceutical preparation as an antitumour agent in treating mammals comprising a therapeutically-effective non-toxic amount of a compound of claim 26.

45. (Previously presented) A method of reducing or inhibiting cancer cell growth in a mammal comprising administering to said mammal an effective amount of an pharmaceutical formulation according to claim 42.

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46. (Cancelled)

47. (Cancelled)

48. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ ,  $R^5$  and  $R^6$  represent a hydrogen atom,  $R^3$  represents a hydrogen atom, X represents a sulfur atom, and  $R^2$  is selected from 3'-Me, 3'-Et, 3'-Br, 3'-Cl, 3'-CN, or 3'-F.

49. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ ,  $R^5$  and  $R^6$  represent a hydrogen atom,  $R^3$  represents a hydrogen atom, X represents an oxygen atom, and  $R^2$  represents 3'-I.

50. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ ,  $R^5$  and  $R^6$  represent a hydrogen atom,  $R^3$  represents 5'-Cl or 5'-Me, X represents an sulfur atom, and  $R^2$  represents 3'-Cl.

51. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ ,  $R^5$  and  $R^6$  represent a hydrogen atom,  $R^3$  represents 5'-Br, X represents an sulfur atom, and  $R^2$  represents 3'-Cl.

52. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents a sulfur atom, wherein  $R^3$ ,  $R^5$  and  $R^6$  each represent a hydrogen atom, Q represents a direct bond, n represents 1,  $R^1$  represents 4-F, and  $R^2$  is selected from 3-CH<sub>3</sub>, a hydrogen atom, 3-I, 3-Cl, or 3-Br.

53. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents a sulfur atom, wherein  $R^3$ ,  $R^5$  and  $R^6$  each represent a hydrogen atom, Q represents a direct bond, n represents 1,  $R^1$  represents 6-F, and  $R^2$  is selected from 3-CH<sub>3</sub>, a hydrogen atom, 3-I, 3-Cl, or 3-Br.

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54. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents a sulfur atom, wherein  $R^3$ ,  $R^5$  and  $R^6$  each represent a hydrogen atom, Q represents a direct bond, n represents 1,  $R^1$  represents 5-F, and  $R^2$  is selected from 3-CH<sub>3</sub>, a hydrogen atom, 3-I, 3-Cl, or 3-Br.

55. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents a sulfur atom, wherein  $R^3$ ,  $R^5$  and  $R^6$  each represent a hydrogen atom, Q represents a direct bond, n represents 1,  $R^1$  represents 7-F, and  $R^2$  represents 3-CH<sub>3</sub>.

56. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents a sulfur atom, wherein  $R^3$ ,  $R^5$  and  $R^6$  each represent a hydrogen atom, Q represents a direct bond, n represents 2,  $R^2$  represents 3-CH<sub>3</sub>, and  $R^1$  represents a 4,5-diF, 4,6-diF, 5-7-diF, or 6,7-diF

57. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents S, Q represents a direct bond, one of  $R^3$  and  $R^6$  represents a hydrogen atom and the other represents -C(O)CH( $R^8$ )NH<sub>2</sub>,  $R^3$  represents a hydrogen atom, n represents 0,  $R^2$  represents a hydrogen atom and  $R^8$  represents a group selected from -CH<sub>3</sub> or -(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>.

58. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents S, Q represents a direct bond, one of  $R^3$  and  $R^6$  represents a hydrogen atom and the other represents -C(O)CH( $R^8$ )NH<sub>2</sub>,  $R^3$  represents a hydrogen atom, n represents 0,  $R^2$  represents 3-CH<sub>3</sub> and  $R^8$  represents a group selected from -CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>, or CH<sub>2</sub>OH.

59. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents S, Q represents a direct bond, one of  $R^3$  and  $R^6$  represents a hydrogen atom and the other represents -C(O)CH( $R^8$ )NH<sub>2</sub>,  $R^3$  represents a hydrogen atom, n represents 0,  $R^2$  represents 3-Cl and  $R^8$  represents a group selected from -CH<sub>3</sub> or -(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>.

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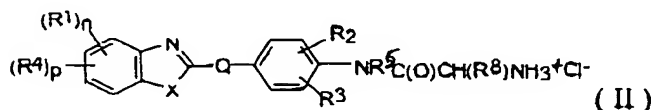
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60. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents S, Q represents a direct bond, one of  $R^5$  and  $R^6$  represents a hydrogen atom and the other represents  $-C(O)CH(R^8)NH_2$ ,  $R^3$  represents a hydrogen atom, n represents 1,  $R^2$  represents 3- $CH_3$ ,  $R^1$  represents 5-F, and  $R^8$  represents a group selected from  $-CH_3$ ,  $-(CH_2)_4NH_2$ , or a hydrogen atom.

61. (New) An arylbenzazole compound of Claim 26 or 27 wherein  $p = 0$ , X represents S, Q represents a direct bond, one of  $R^5$  and  $R^6$  represents a hydrogen atom and the other represents  $-C(O)CH(R^8)NH_2$ ,  $R^3$  represents a hydrogen atom, n represents 1,  $R^2$  represents 3- $CH_3$ ,  $R^1$  represents 6-F, and  $R^8$  represents a group selected from  $-CH_3$ ,  $-(CH_2)_4NH_2$ , or a hydrogen atom.

62. (New) An arylbenzazole compound represented by the structural formula II below, or a pharmaceutically acceptable salt thereof



wherein

X represents S or O;

$R^1$  independently represents fluoro, iodo or trimethyltin;

$R^2$  represents hydrogen,  $NO_2$ ,  $N_3$ , halogen, alkyl, a halo substituted or hydroxy substituted alkyl, CN or  $CF_3$ ;

$R^3$  represents hydrogen, halogen, alkyl, or a halo substituted or hydroxy substituted alkyl;

$R^4$  independently represents alkyl, a halo substituted or hydroxy substituted alkyl, hydroxyl, alkoxy or aralkoxy;

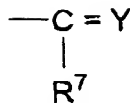
$R^5$  represents hydrogen, an amino acid, an alkyl, or a group



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wherein Y represents O or S, and R<sup>7</sup> represents alkyl or -CH(R<sup>8</sup>)NH<sub>2</sub> where R<sup>8</sup> represents hydrogen, or an optionally substituted alkyl;

Q represents a direct bond, -CH<sub>2</sub>- or -CH=CH-;

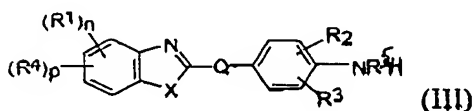
p represents zero, 1 or 2; and

n represents zero, 1, 2 or 3;

subject to the following provisos:

- (a) alkyl or substituted alkyl groups include linear, branched or cyclic structures but when present as linear or branched structures in the compound or as a moiety in another group such as alkoxy they are composed of less than ten carbon atoms;
- (b) p represents zero or 1 when n represents 3;
- (c) when a group is optionally substituted, unless otherwise specified, the substituent is selected from one or more of the following: a halogen, OH, SH, NH<sub>2</sub>, COOH and CONH<sub>2</sub>.

63. A method of preparing the compound of claim 62 comprising reacting a compound of formula III below



with a BOC-protected amino acid, followed by hydrochloric acid.